Suppression of Alk8-mediated Bmp signaling cell-autonomously induces pancreatic beta-cells in zebrafish.

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Scientific Abstract:
Bmp signaling has been shown to regulate early aspects of pancreas development, but its role in endocrine, and especially beta-cell, differentiation remains unclear. Taking advantage of the ability in zebrafish embryos to cell-autonomously modulate Bmp signaling in single cells, we examined how Bmp signaling regulates the ability of individual endodermal cells to differentiate into beta-cells. We find that specific temporal windows of Bmp signaling prevent beta-cell differentiation. Thus, future dorsal bud-derived beta-cells are sensitive to Bmp signaling specifically during gastrulation and early somitogenesis stages. In contrast, ventral pancreatic cells, which require an early Bmp signal to form, do not produce beta-cells when exposed to Bmp signaling at 50 hpf, a stage when the ventral bud-derived extrapancreatic duct is the main source of new endocrine cells. Importantly, inhibiting Bmp signaling within endodermal cells via genetic means increased the number of beta-cells, at early and late stages. Moreover, inhibition of Bmp signaling in the late stage embryo using dorsomorphin, a chemical inhibitor of Bmp receptors, significantly increased beta-cell neogenesis near the extrapancreatic duct, demonstrating the feasibility of pharmacological approaches to increase beta-cell numbers. Our in vivo single-cell analyses show that whereas Bmp signaling is necessary initially for formation of the ventral pancreas, differentiating endodermal cells need to be protected from exposure to Bmps during specific stages to permit beta-cell differentiation. These results provide important unique insight into the intercellular signaling environment necessary for in vivo and in vitro generation of beta-cells.

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